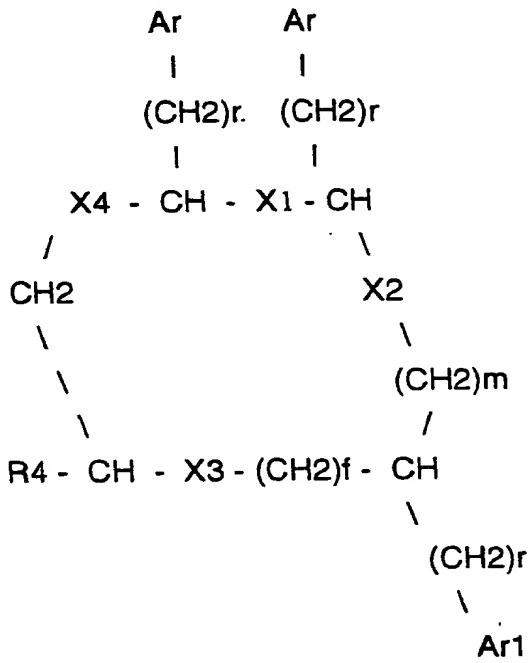
MONOCYCLIC COMPOUNDS HAVING NK-2 ANTAGONIST ACTION AND COMPOSITIONS CONTAINING THEM.

Field of the invention

The present invention refers to compound of general formula (I)



(I)

wherein:

X_1, X_2, X_3, X_4, same or different, are a group chosen among: -CONR-, -NRCO-, $-CH_2$-NR-, -NR-CH_2- where R is H , C_{1-3} alkyl, benzyl;

f, m, same or different, are a number chosen among 0,1 and 2;

R_1 and R_2, same or different, are a group:

$-(CH_2)_r$ -Ar where r = 0, 1, 2 and Ar is an aromatic group chosen among: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, possibly substituted with up to 2 substituents chosen among C_{1-3} alkyl, haloalkyl, C_{1-3} alkyloxy, C_{2-4} amino-alkyloxy, halogens, OH, NH_2, CN, NR_6R_7, where R_6 ed R_7, same or different, are H or C_{1-3} alkyl,

R_3 is a group chosen among the following groups:

- $(CH_2)_r$-Ar_1 where r = 0, 1, 2 and Ar_1 is an aromatic group chosen among: benzene, naphtalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, possibly substituted with up to 2 grou AMENDED SHEET C_{1-3} alkyl and haloalkyl, C_{1-3}

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alkyloxy and amino-alkyoxy, halogens, OH, NH_2, NR_6R_7, where R_6 and R_7, same or different, are H or C1-3 alkyl,

R_4 is a group chosen among:

- NR_8R_9, where R_8 is H or C_{1-3} alkyl and

R_9 is

(i) a methanesulfonyl, tosyl, tetrahydropyranyl,

(ii) tetrahydrothiopyranyl possibly mono or di-substituted by oxygen on the S atom,

(iii) piperidyl possibly substituted on the N-atom by a C_{1-3} alkyl, C1-3 acyl, aminosulfonyl, methanesulfonyl;

(iv) a group $(CH2)g-R_{10}$ where g is 1,2,3 and R_{10} is chosen among morpholine, furan, CN;

or R_8 and ~~R_9~~ together with the N atom to which they are linked form a piperazine possibly substituted on ~~one~~ of its nitrogen by C_{1-3} alkyl, C1-3 acyl or methanesulfonyl;

- $N(R_{11})CO(CH_2)h-R_{12}$ where R_{11} is H, C_{1-3} alkyl; h is 0,1,2,3; and R_{12} is chosen among: morpholine, pyrrolidine possibly substituted with an hydroxy or an hydroxymethyl, piperidine possibly substituted with a group hydroxy, carboxyamido or aminosulfonyl, piperazine possibly substituted on the N-atom by C_{1-3} alkyl, triazole, tetrazole, 5-mercapto-tetrazole, furan, thiophene, thiomorpholine possibly mono or di-oxygenated on the S-atom, amino-cyclohexane possibly substituted by an hydroxy group.

$-COR_{13}$ wherein R_{13} is morpholine or piperazine possibly substituted with a C_{2-6} alkyl containing one or more ether or hydroxy groups.

Since compounds of formula (I) present various chiral centers the present invention obviously refers also to the single enantiomers and to the diastereoisomers mixtures.

State of the art

The NK2 receptor of tachykinins is widely present in the peripheral nervous system in mammals. One of the various effects of the selective stimulation of the NK2 receptor is the contraction of smooth muscles. Therefore the antagonists of the NK2 receptor are agents capable of controlling the excessive contraction of smooth muscles in all those pathologic condition where the release of tachykinins

contributes to the genesis of the corresponding pathological disorder.

More particularly the broncospastic component of asthma, cough, pulmonary irritations, intestinal spasms or local spasms in bladder and ureter in the case of cystitis, infections and kidney colics can be considered conditions where the administration of NK2 antagonists is appropriated (E.M. Kudlacz et al. Eur. J.

Pharmacol., 1993 36, 17-25).

Cyclic compounds, in particular cyclic hexapeptides, cyclic (A.T. McKnight et al. Br. J. Pharmacol. 1991, 104, 355) and bicyclic (V. Pavone et al. WO 93/212227), or cyclic pseudopeptides (L. Quartara et al. J. Med. Chem., 1994, 37, 3630; S. L. Harbeson et al. Peptides, Chemistry and Biology. Proceedings of Twelth American Peptide Symposium, 1992, 124) are known in literature for their strong antagonistic activity on the NK-2 receptor of tachykinins.

In WO9834949 it is described how compounds having lower molecular weight, monoyclic, containing only four bi-functional residues linked among each other by a peptide or pseudopeptide bond present pharmacological activity similar or higher than that of known compounds and moreover show a high selectivity for the human NK2 receptor.

It is an object of the present invention to make available new monocyclic compounds having four bi-functional residues and presenting new substituents not described in WO98/34949. These compounds are new interesting powerful antagonists to NK2 receptor and therefore are useful for the treatment of pathologies connected with such interaction moreover they show an in vitro and in vivo activity largely higher than that shown by the most similar compounds described in WO98/34949.

Detailed description of the invention

The present invention makes available new monocyclic compounds of general formula (I) as above defined containing four residues linked to each other by a peptide or pseudopetide bond having an antagonistic action on the NK2 receptor.

The present invention refers also to the pharmaceutically acceptable salts of the above said compounds, to processes for their preparation and to pharmaceutical compositions containing them.

Since the compounds of formula (I) present chiral centers the present invention refers also to the corresponding enatiomers and the mixture of diastereoisomers.

Preferred compounds according to the present invention are those wherein in formula (I):

f is 1

m is 0

X_1, X_2, X_3, X_4, same or different are a group -CONR- and -NRCO-,

R is H or methyl

R_1 and R_2 same or different, are::

-(CH_2)-Ar wherein Ar is an aromatic group chosen among benzene, pyridine, indole, possibly substituted up to two residues with substituents chosen among: C_{1-3} alkyl, ~~and haloalkyl,~~ C_{1-3} alkyloxy, C_{2-4} amino alkyloxy, halogens, OH, NH_2, CN, NR_6R_7, where R_6 and R_7, same or different, are H or C_{1-3} alkyl;

R_3 is a group chosen among:

- CH_2-Ar_1 wherein Ar_1 is an aromatic group chosen among: alfa naphthyl, beta naphthyl, phenyl, phenyl substituted up to two residues chosen among C_{1-3} alkyl, ~~and haloalkyl~~, C_{1-3} alkyloxy, halogens, OH, NH_2,

R_4 is a group chosen among:

- NR_8R_9, where R_8 is H or C_{1-3} alkyl and

R_9 is chosen among: methanesulfonyl, tosyl, tetrahydropyranyl, tetrahydrothiopyranyl possibly mono or di-substituted by oxygen on the S atom, piperidyl possibly substituted on the N-atom by a C_{1-3} alkyl, C1-3 acyl, aminosulfonyl, methanesulfonyl; or a group (CH2)g-R_{10} where g is 1,2,3 and R_{10} is chosen among morpholine, furan, CN;

or R_8 and R_9 together with the N atom to which they are linked form a piperazine possibly substituted on the N atom with a C1-3alkyl, C1-3 acyl or methanesulfonyl;

- $N(R_{11})CO(CH_2)_h$-R_{12} where R_{11} is H, C_{1-3} alkyl; h is 0,1,2,3; and R_{12} is chosen among: morpholine, pyrrolidine possibly substituted with an hydroxy or hydroxymethyl, piperidine possibly substituted with a group hydroxy, carboxyamido or aminosulfonyl, piperazine possibly substituted on the N-atom by C_{1-3} alkyl, triazole, tetrazole, 5-mercapto-tetrazole, furan, thiophene, thiomorpholine possibly mono or di-oxygenated on the S-atom, amino- cyloh xane possibly substituted by an hydroxy group.

- COR_{13} wherein R_{13} is a group chosen among morpholine and piperazine possibly substituted by a C_{2-6} alkyl containing one or more ether or hydroxy

groups.

More preferred are the compounds of formula (I) wherein:

- X_1, X_2, X_3, X_4 are ~~-CONR-~~ CONH

- ~~R is H;~~

- R1 is the lateral chain of triptophane;

- R2 is the lateral chain of phenylalanine possibly substituted with up to two residues chosen among: chlorine, fluorine, CF_3, OH, CN ; or a group 3-pyridyl-methyl, 4-pyridyl-methyl;

- R3 is benzyl.

and the other substituents are as above defined.

An even more preferred group of compounds according to the invention are those wherein R, R1, R2, R3, f, m are as above defined and:

R4 is a group NR8R9 wherein:

R8 is H or methyl;

R9 is a group chosen among: : 4-tetrahydropyranyl, 4-tetraidrothiopyranyl, 1-oxo-tetraidrothiopyran-4-yl, 1,1-dioxo-tetrahydrothiopyran-4-yl, N-methyl-4-piperidinyl, N-methansulfonyl-4-piperidinyl, N-aminosulfonyl-4-piperidinyl,

or R8 and R9 together with the N atom to which they are linked represent: N-methyl-piperazinyl, N-acetyl-piperazinyl, piperazinyl, N-methanesulfonyl-piperazinyl.

Among this last group of compounds the following are especially preferred:

i) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

ii) cyclo{Suc[1-(S)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

iii) cyclo{Suc[1-(R)-(1-methyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

iv) cyclo{Suc[1-(R)-(4-tetrahydrothiopyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

v) cyclo{Suc[1-(R)-(1-oxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

vi) cyclo{Suc[1-(R)-(1,1-dioxo- tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

vii) cyclo{Suc[1-(R)-N-methyl-N-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

viii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Tyr-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

ix) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-F)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

x) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(3,5-F)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xi) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CN)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CF3)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xiii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(4-pyridyl)-[R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xiv) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(3-pyridyl)-[R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xv) cyclo{Suc[1-(R)-(1-methylsulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xvi) cyclo{Suc[1-(R)-(1-aminosulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xvii) cyclo{Suc[1-(R)-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xviii) cyclo{Suc[1-(R)-4-methyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xix) cyclo{Suc[1-(R)-4-acetyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xx) cyclo{Suc[1-(R)-4-methanesulfonyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

Among the compounds of formula (I) wherein R, R1, R2, R3, f, m are as hereabove defined preferred are also those wherein:

R_4 represents a group NR_8R_9, where R_8 is H and R9 is chosen among: methanesulfonyl, tosyl, a group $(CH2)g\text{-}R_{10}$ wherein g is 1, 2 and R_{10} is chosen among: morpholine, furan, CN.

Among this last group of compounds particularly preferred are:

xxi) cyclo{Suc[1-(S)-4-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxii) cyclo{Suc[1-(R)-4-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxiii) cyclo{Suc[1-(S)- (4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxiv) cyclo{Suc[1-(R)- (4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxv) cyclo{Suc[1-(S)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxvi) cyclo{Suc[1-(R)-2-(4- morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxvii) cyclo{Suc[1-(R)-(2-furyl)methylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxviii) cyclo{Suc[1-(R)-cianomethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

Another preferred selection of the compound of formula (I) wherein R, R1, R2, R3, f, m are as previously defined, those wherein:

R4 represents a group $-N(R_{11})CO(CH_2)_h\text{-}R_{12}$ wherein R_{11} is H, h is 0 or 1, and R12 is chosen among. : 1-tetrazolyl, 5-mercapto-tetrazol-1-yl, 1-triazolyl, furanyl, thiophenyl, morpholine, 4-hydroxy-piperidine, 4-carboxyamido-piperidine, 3-hydroxy-pyrrolidine, 2-hydroxymethylpyrrolidine, 4-methyl-piperazine, 4-aminosulfonyl-piperazine, 1-oxo-thiomorpholin , 4-hydroxy-cycloh xan-1-yl-amino

Among the compounds of this last group particularly preferred are:

xxix) cyclo{Suc[1-(R)-2-(4-morpholino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxx) cyclo{Suc[1-(S)-2-(4- morpholino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxi) cyclo{Suc[1-(S)-2-(tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxii) cyclo{Suc[1-(R)-2-(tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxiii) cyclo{Suc[1-(S)-2-(5-mercapto-tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxiv) cyclo{Suc[1-(R)-2-([1,2,4]triazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxv) cyclo{Suc[1-(R) -(furan-2-yl)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxvi) cyclo{Suc[1-(R)-2-(thiophen-3-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxvii) cyclo{Suc[1-(R)-(4-morpholino)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxviii) cyclo{Suc[1-(R)-2-(4-hydroxy-piperidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxxix) cyclo{Suc[1-(R)-2-(4-aminocarbonyl-piperidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xl) cyclo{Suc[1-(R)-2-(3-hyroxy-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xli) cyclo{Suc[1-(R)-2-(2-(S)-hydroxymethyl-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlii) cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xliii) cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xliv) cyclo{Suc[1-(R)-2-(4-aminosulfonyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlv) cyclo{Suc[1-(R)-2-(1-oxo-thiomorpholin-4-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlvi) cyclo{Suc[1-(R)-2-*(trans*-4-hydroxy-cyclohexan-1-yl-amino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

Another preferred selection of compounds of formula (I) wherein R, R1, R2, R3, f, m are as above defined are those wherein:

R4 is a group COR_{13} wherein R_{13} is a group chosen among: morpholine and 4-(hydroxyethyloxyethyl)-piperazine.

Among this last group of compounds especially preferred are:

xlvii) cyclo{Suc[1-(4- morpholine)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xlviii) cyclo{Suc[1-(4-hydroxyethyloxyethyl-piperazin-1-yl)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

Phamaceutically acceptable salts of compounds of formula (I) are for example the salts with inorganic acids (as hydrochloric, hydrobromic, hydroiodic, sulphuric, nitric, phosphoric) or organic acids (as acetic, propionic, succinic, malonic, citric, tartaric, methanesulfonic, p-toluensulfonic).

According to the invention the compounds of formula (I) containing peptide or pseudopeptide bonds can be obtained by the normal condensation reactions according to known techniques. A general method of preparation of peptid compounds (X_1-X_4 = -CONR-, -NRCO-) is for example to synthetise in a solution the linear peptide chain using the appropriate aminoacids, carboxylic or diamino derivatives suitably protected, and after selective de-protection of the terminal C- and N- chains, to cyclise in polar organic solvents in a diluted solution. For the activation of the carboxylic group normally th methods using EDCI.HCl and HOBt or PyBOP and DIEA in DMF are pref rred.

The dicarboxylic precursors containing the R_4 group and the diamino precursors containing the R_3 group were prepared according to the methods described in literature.

In particular in the synh sis of derivatives wherein R_4 = amino or carboxylic group, suitably protected aspartic or carbosuccinic acid were used respectively (E. Perrotta et al, Synlett, 1999, 144-146). The synthesis of the ethylendiamine derivatives containing the R_3 groups was performed according to G. Kokotos et al., J. Chem. Research (S), 1992, 391.

The compounds of formula (I) as above described are powerful antagonists of NK2 receptor of tachykinins and can be administered as agents capable of controlling the excessive smooth muscular contraction in whatever pathological condition where the release of tachykinins contributes to the pathology.

In particular the broncospastic component of asthma, cough, pulmonary irritation, the intestinal spasms or local spasms of bladder and ureter during cystitis, infections and kidneys colics, can be considered conditions where the administration of compounds of formula (I) as NK2 antagonists, can be appropriate.

The compounds of formula (I) object of the present invention are useful for the administration to superior animals and humans by parenteral, oral, by inhalation, sublingual administration giving pharmacological effects thanks to their properties.

For the parenteral administration (intravenous, intramuscular and intradermal) sterile solutions or lyophilised preparations are used.

For nasal, by inhalation or sublingual administration aqueous solutions, aerosol, powders or capsules are used as appropriate.

The quantity of active principle administerd with the above said formulations is normally comprised between 0.1 and 10 mg/kg of patient body weight.

Hereinafter some specific examples of compounds according to the invention are reported.

EXAMPLE 1: cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein X_1 = X_2 = X3 = X_4 = -CO-NH-; R_1 = -CH_2-(indol-3-yl); R_2 = R_3 = -CH_2-C_6H_5; R4 = (4-tetrahydropyranyl)amino; m = 0, f = 1; the carbon atoms C-R_1 and C-R_2 have configuration S, while C-R_3 and C-R_4 have configuration R).

As starting compound AMENDED SHEET c[1-(R)-amino]-Trp-Phe-[(R)-NH-

CH($CH_2C_6H_5$)-CH_2-NH]-} (Compound A).

(compound of formula (I) wherein: X_1 = X_2 = X3 = X_4 = -CO-NH-; R_1 = -CH_2-(indol-3-yl); R_2 = R_3 = -CH_2-C_6H_5; R_4 = -NH_2; m = 0, f = 1; the carbon atoms C-R_1 and C-R_2 have configuration S, while C-R_3 and C-R_4 have configuration R) is used . The compound A is prepared as follow:

a) Synthesis of dipeptide Boc-Trp-Phe-OH

To a solution of H-Trp-Phe-OH (5 g,) in dioxane (30 ml), H_2O (15 ml) and NaOH 1M (15.6 ml), cooled at 0-5°C, under stirring, of-tert-butyldicarbonate (3.4 g) was added. The reaction mixture was left under stirring for 2 h, concentrated, and extracted with pentane (2 x 20 ml). The aqueous phase was cooled with ice, added wit AcOET (50 ml), acidified with $KHSO_4$ up to pH 2-3, separated and extracted with AcOEt (2 x 50 ml). The organic phases pooled together were washed with brine (50 ml), dried and evaporated under vacuum at 30°C, giving 6 g of the desired compound as a white semisolid residue.

TLC: Rf 0.55 (chloroform/cyclohexane/AcOH/H_2O = 45/45/5/5), 0.52 ($CHCl_3$/ MeOH = 9/1)

b) Synthesis of (R)-1-benzyl-2-(N-benzyloxycarbonylamino)ethylamina

(R)-1-benzyl-1-(N-*tert*-butyloxycarbonylamino)ethylamina, prepared as described in G. Kokotos et al., J. Chem. Research (S), 1992, 391, was transformed into the corresponding (R)-benzyl-1-(N-*tert*-butyloxycarbonylamino)-2-(benzyloxycarbonylamino)ethylamina and this into (R)-1-benzyl-2-(N-benzyloxycarbonylamino)ethylamina according to the usual methods of protection and deprotection of aminoacids.

c) Synthesis of Boc-Trp-Phe-[(R)-NH-CH(CH2-C_6H_5)-CH_2-NH-Z]

To a solution of Boc-Trp-Phe-OH (1.19 g, 2.63 mmoli) in anhydrous DMF (10 ml) (R)-1-benzyl-2-(benzyloxycarbonylamino)ethylamine (750 mg), PyBOP (1.37 g) e DIEA (0.9 ml) were added under nitrogen. The reaction mixture was left under stirring for a night at room, added with AcOEt (80 ml), washed with HCl 1N (3 x 30 ml), Na_2CO_3 5% (3 x 30 ml) and H_2O (30 ml). The organic phase was evaporated under vacuum at 30°C, giving 1.8 g of ivory colored solid residue.

The crude was purified by washing in a warm AcOEt suspension followed by

MeOH washing at room temperature giving 1.15 g of the desired compound as a white solid. MS (TS) : $[MH^+]$ = 718

d) Synthesis of H-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-Z]

To a suspension of the previously obtained compound (1.0 g) in CH_2Cl_2 (25 ml) TFA (15 ml) was added under stirring at 0°C. The reaction mixture was left under stirring for 30 minutes at 0°C and for 2 h at room temperature, the formation of the precursor is checked by HPLC.

After evaporating the solvent the residue was recovered with AcOET (100 ml), washed with $NaHCO_3$ 5% (2 x 30 ml) and brine (30 ml).

The organic phase was dried with $MgSO_4$ and evaporated under vaccum at 30°C giving 650 mg of the desired compound.

e) Synthesis of Boc-(D)-Asp{Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2-NH-Z}-OBzl

To a solution of Boc-(D)Asp-OBzl (690 mg), HOBt (850 mg) e EDCI.HCl (450 mg) in anhydrous DMF (50 ml) a solution of the compound of Example 1(d) (1,3 g) was added under stirring at room temperature.

The reaction mixture was left under stirring at room temeprature for 4 h.After evaporation of the solvent (under vacuum) the residue was treated with $KHSO_4$ aq. 5% giving a solid which was filtered, washed with $NaHCO_3$ aq. 5%, water, and thereafter dried the product was crystallized from ethanol giving 850 mg of the desired compound as a white solid.

MS (ES+): [MH+] = 923; HPLC (Method A1): rt = 21.1 min.

f) Synthesis of Boc-(D)-Asp{Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2-NH_2]}-OH

The compound of example 1e (800 mg) was solubilised in DMF (10ml) and diluted with MeOH (40 ml), thereafter hydrogenated in the presence of Pd/C 10% (100 mg) at room pressure and temperature for 5 h. The catalyst was filtered and washed with MeOH. After evaporation of the solvent 500 mg of the desired product were obtained as a white solid.

MS (ES+): [MH+] = 663; HPLC (Method A2): rt=10.4 min.

Synthesis of cyclo{-Suc[1(R)NHBoc]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2-NH]}

To a solution of the compound according to example 1 (f) (800 mg) in anhydrous DMF (200 ml) 465 mg of HOBt and 224 mg of EDCI.HCl were added under stirring

and in nitrogen current. The reaction mixture was left under stirring for 5 h and after evaporation of the solvent the residue was solved in ethyl acetate and the organic phase was washed with an aqueous solution of KHSO4 5%, NaHCO3 5% and brine, thereafter was dried and evaporated, the recovered yellow solid (600 mg) was crystallized in isopropanol/water: 1/1 giving 450 mg of a white solid.
MS (ES+): [MH+] = 681; HPLC (Method A2): rt=14.7 min..

Synthesis of cyclo{Suc[1(R)NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2-NH]} (= Compound A)

To a suspension of the compound of EXAMPLE 1g (400 mg) in CH_2Cl_2 (40 ml), TFA (13 ml) was added at 0°C under stirring. The reaction was carried on for 2 h at room temperature. The solvent was evaporated and the residue treated with $NaHCO_3$ and water and extracted in ethyl acetate. The organic phase was washed with brine, dried and evaporated giving 320 mg of a solid product.
MS (ES+): [MH+] = 581; HPLC (Method A2): rt=12.4 min.

A sample of 20 mg was purified by preparative HPLC giving 15 mg of trifluoroacetate: cyclo{-Suc[1(S)NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.TFA

MS (ES+): [MH+] = 581; HPLC (Method A2): rt=12.4 min; 1H-NMR 500 MHz (DMSO): d 2.21 (dd, J = 6.1, 14.3 Hz) 2.68-2.82 (m, 6H), 2.95 (dd, J = 3.0, 14.4 Hz, 1H), 3.08 (bd, J = 12.0 Hz, 1H), 3.38 (dd J = 3.8, 14.2 Hz, 1H), 3.48-3.56 (m, 2H), 3.98-4.08 (m, 1H), 4.11-4.17 (m, 1H), 4.20-4.28 (1H, m), 6.71 (d, J = 9.1 Hz, 1H), 6.98 (t, J = 9.1 Hz, 1H), 7.04-7.09 (m, 1H), (m, 2H), 7.15-7.21 (m, 4H,), 7.21-7.30 (m, 6H), 7.33 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 7.8 Hz), 7.67 (bs, 1H), 7.82 (bs, 1H), 8.63 (d, J = 5.2, 1H), 10.81 (d, J = 1.3 Hz, 1H).

k) 50 mg of Compound A prepared as described in EXAMPLE 1a-1h, were solved in 5 ml methanol. Acetic acid (0.1 ml), tetrahydro-4H-pyran-4-one (18 mg solved in 1 ml of methanol) and sodium cianoborohydride (12 mg) are added in the given order. The mixture is kept for one night under stirring, acidified with HCl 1N up to pH=1-2, diluted with water; the methanol is evaporated, $NaHCO_3$ is added and the solution is extracted with ethyl acetate, washing with brine and drying on sodium sulfate. The solution is concentrated and purified by preparative HPLC (Method P1).

1H-NMR (DMSO-d6, 500 MHz): d 1.57 (2H, bs); 1.90-2.04 (2H, m); 2.38-2.47 (1H, m); 2.67-2.98 (5H,m); 3.06-3.25 (4H, m); 3.25-3.42 (m, sovrapposto al segnale dell'acqua); 3.72 (1H, bs); 3.82-3.95 (2H, m); 3.95-4.11 (2H, m); 4.25 (1H, bs); 4.33 (1H, m); 6.86 (1H, d, J = 8.4 Hz); 6.97- 7.03 (1H, m); 7.04-7.31 (12H, m); 7.35 (1H, d, J = 8.1 Hz); 7.41-7.51 (1H, bs); 7.43 (1H, d, J = 7.9 Hz); 8.82-9.11 (3H, m); 10.85 (1H, d, J = 1.0 Hz).

MS: m/z : 665.4 (MH^+).

By similar procedure the following compounds were obtained:

EXAMPLE 2: cyclo{Suc[1-(S)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2NH$]}

(compound of general formula (I) wherein C-R4 has S configuartion, R4 is (4-tetrahydropyranyl)amino and the other substituents are as described for Compound A).

The compound is obtained according to the procedure of Example 1 but the starting product is the isomer of Compound A having S configuration at the C-R4.

HPLC (Method A2): rt = 12.8 min

MS: m/z : 665.4 (MH^+).

EXAMPLE 3: cyclo{Suc[1-(R)-(1-methyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2NH$]}

(compound of general formula I wherein R4 is (1-methyl-piperidin-4-yl)amino and the other substituents are as described for Compound A.

The compound is prepared as in example 1 but using as reagent 1-methyl-4-piperidone.

1H-NMR (DMSO-d6, 500 MHz): d 1.75 (2H, bs); 2.17 (1H, bs); 2.25 (1H, bs); 2.34-2.38 (1H, m); 2.69-3.05 (m overlapped at bs); 2.75 (s); 3.05-3.58 (m, overlapped to the water signal); 3.70 (1H, bs); 3.93-4.10 (2H, bs); 4.10-4.39 (2H, bs); 6.85 (1H, d, J = 8.4 Hz); 7.00 (1H, m); 7.05-7.36 (12H, m); 7.36 (1H, d, J = 8.1 Hz); 7.43 (1H, bs); 7.49 (1H, d, J = 8.0 Hz); 8.94 (1H, bs); 9.26 (1H, bs); 9.72 (1H, bs); 10.90 (1H, s).

MS: m/z = 678, MH^+.

EXAMPLE 4: cyclo{Suc[1-(R)-(4-tetraidrotiopyranil)amino]-Trp-Phe-[(R)-NH-

$CH(CH_2-C_6H_5)-CH_2NH]\}$

(compound of formula I wherein R4 is (4-tetrahydrothiopyranyl)amino and the othe substituents are as described for compound A).

The compound is prepared according to Example 1 but using as reagent tetrahydro-thiopyran-4-one.

MS: m/z = 681, MH^+.

EXAMPLE 5: cyclo{Suc[1-(R)-(1-oxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2NH$]}

(compound of general formula I wherein R4 is (1-oxo-4-tetrahydrothiopyranyl)amino and the other substituents are the same of Compound A).

The compound is prepared as in example 1 but using as reagent 1-oxo-tetrahydro-thiopyran-4-one.

HPLC (Method A2): rt = 12.7 min.

MS: m/z = 697.3 (MH^+).

EXAMPLE 6: cyclo{Suc[1-(R)-(1,1-dioxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2NH$]}

(compound of general formula I wherein R4 is (1,1-dioxo-4-tetrahydrothiopyranil)amino and the other substituents are the same of Compound A).

The compound is prepared as in example 1 but using as reagent 1,1-dioxo-tetrahydro-thiopyran-4-one.

HPLC (Method A2): rt = 13.7 min.

MS: m/z = 713.2 (MH^+).

EXAMPLE 7: cyclo{Suc[1-(R)-N-methyl-N-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-$CH(CH_2-C_6H_5)-CH_2NH$]}

(compound of general formula I wherein R4 is N-methyl-N-(4-tetrahydropyranyl)amino and the other substituents are the same of Compound A).

50 mg of the compound described in Example 1 are solved in 5 ml of anhydrous methanol. Acetic acid (0.1 ml), paraformaldheyde (60 mg) and sodium

cianoboroidride (40 mg) are added in the given sequence. The mixture is left under stirring for a night, acidified with HCl 1N up to pH=1-2, diluted with water and the methanol is evaporated; $NaHCO_3$ is added and then the solution is extracted with ethyl acetate, the extracted is dried on sodium sulfate. The soluton is concentrated and purified by preparative HPLC (Method P2).

HPLC (Method A2): rt = 13.7 min.

MS: m/z = 679.3 (MH^+).

EXAMPLE 8: cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Tyr-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein cui R_2 = 4-hydroxybenzyl, R4 = (4-tetrahydropyranyl)amino and the other substituents are as defined for Compound A).

The compound is prepared according to Example 1(b)-1(k) but Boc-Trp-Tyr(OBzl)-OH is used instead of Boc-Trp-Phe-OH.

HPLC (Method A2): rt = 11.0 min.

MS: m/z = 681.3 (MH^+).

EXAMPLE 9: cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-F)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein cui R_2 =4-fluorobenzyl, R4 = (4-tetrahydropyranyl)amino and the other substituents are as defined for Compound A).

The compound is prepared according to Example 1(b)-1(k) but Boc-Trp-Phe(4-F)-OH is used instead of Boc-Trp-Phe-OH.

HPLC (Method A2): rt = 13.7 min.

MS: m/z = 683.3 (MH^+).

EXAMPLE 10: cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(3,5-F)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein cui R_2 = 3,5-difluorobenzyl, R4 = (4-tetrahydropyranyl)amino and the other substituents are as defined for Compound A).

The compound is prepared according to Example 1(b)-1(k) but Boc-Trp-Phe(3,5-F)-OH is used instead of Boc-Trp-Phe-OH.

HPLC (Method A2): rt = 14.3 min.

MS: m/z = 701.2 (MH^+).

EXAMPLE 11: cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CN)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

To 377 mg of Boc-(S)-4-ciano-phenylalanine, solved in 8 ml of DMF, HOBt (470 mg), EDCI.HCl (330 mg) and 630 mg of (R)-1-benzyl-2-(N-fluorenylmethyloxycarbonylamino)ethylamina trifluoroacetate (prepared according to Example 1(b)), solved in 8 ml of DMF are added in the given order. DIEA (0.38 ml) is added drop by drop maintaining under stirring for 3 h. The solution is dried and the residue is treated with citric acid 105 and water; the precipitated solid is filtered, washed with water, NaHCO3 5%, water and dried. The obtained solid (790 mg) is suspended in dichlorometane (6.5 ml).

The suspension is cooled at 0°C, (3.5 ml) is added and the tempearure is raised at room temperature maintaining under stirring for 1 h. The solution is concentrated to dryness and the residue is treated with ethyl ether, under stirring, the formed solid is filtered and washed with ether.

After drying the obtained solid (550 mg) is solved in 8 ml of DMF are added to a solution of DMF (6 ml), Boc-Trp-OH (250 mg), HOBt (216 mg), EDCI.HCl (200 mg). DIEA (0.23 ml) is added drop by drop and the solution is stirred for 1 h. The solution is concentrated to dryness and the residues treated with water and citric acid, under stirring; the formed solid is filtered and washed with water, NaHCO3 5%, water; 623 mg of a solid compound are obtained.

The obtained solid is solved in DMF (15 ml); diethylamine (1.5 ml) is added and the solution is stirred for 2 h. The solvent is evaporated and the residue is treated with diethylether under stirring, the formed solid is filtered and washed with diethylether obtaining 220 mg of a solid product.

The product is solved in 4 ml of DMF and added drop by drop to a solution of Fmoc-D-Asp-(OtBu)-OH (150 mg), HOBt (115 mg), EDCI.HCl (84 mg) in DMF (4 ml).

The solution is maintained 2 h under stirring, concentrated to dryness and the residue is treated with citric acid 10 % and water; the formed solid is filtered, washed with water, NaHCO3 al 5%, water and dried, 340 mg of a solid product are obtained.

The obtained product is suspended in dichloromethane, ethanediol (0.035 ml) and, at 0°C, TFA (4 ml). The temperature is brought to room temperature under stirring for 1 h. the solution is dried and the residue is treated with diethylether under stirring, the formed solid is filtered and washed with diethylether.

After drying 280 mg of solid product are obtained.

The product is solved in 30 ml of DMF, HOBt (185 mg) and EDCI.HCl (160 mg) are added and the solution is maintained under stirring for 5 h and then left staying for one night. The solution is concentrated and the residue is treated with citric acid 10% and water, the formed solid is filtered. Washed with water, NaHCO3 5%, water and dried giving 220 mg of a solid product.

The obtained solid is solved in DMF (10 ml); added with diethylamine (1.0 diethylether under stirring, the formed solid is filtered, washed with diethylether giving 157 mg of a solid product.

The obtained product is solved in methanol (13 ml) and added with acetic acid (0.26 ml), tetrahydro-4H-pyran-4-one (80 mg) and sodium cianoborohydride (55 mg) in the given order. The solution is kept under stirring overnight, acidified with HCl 1N up to pH=1-2, stirred for 1 h, methanol is evaporated and $NaHCO_3$ is added, the solution is extracted with ethylacetate and dried on sodium sulfate.

The solution is concentrated and purified by preparative HPLC (Method P3).

MS: m/z = 690.2 (MH^+).

HPLC (Method A2): rt = 12.7 min.

EXAMPLE 12: cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CF3)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of formula I wherein R_2 = (4-trifluoromethyl)benzyl, R4 = (4-tetrahydropyranyl)amino and the other substituents are as in Compound A.

The compound is prepared according to Example 1(b)-1(k) but using Boc-Trp-Phe(4-CF3)-OH instead of Boc-Trp-Phe-OH.

HPLC (Method A2): rt = 15.4 min.

MS: m/z = 733.2 (MH^+).

EXAMPLE 13: cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(4-pyridyl)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of formula I wherein R_2 = 4-pyridylmethyl, R4 = (4-tetrahydropyranyl)amino and the other substituents are as in Compound A.

The compound is prepared according to Example 11 but using Boc-(S)-3-(4-pyridyl)alanine instead of Boc-(S)-4-ciano-phenylalanine.

HPLC (Method A2): rt = 6.9 min.

MS: m/z = 666.3 (MH^+).

EXAMPLE 14: cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(3-pyridyl)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R_2 = 3-pyridylmethyl, R4 = (4-tetrahydropyranyl) and the other substituents are as in Compound A.

The compound is prepared according to Example 11 but using Boc-(S)-3-(3-pyridyl)alanine instead of Boc-(S)-4-ciano-phenylalanine.

HPLC (Method A2): rt = 7.3 min.

MS: m/z = 666.3 (MH^+).

EXAMPLE 15: cyclo{Suc[1-(R)-(1-methylsulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of formula I wherein R4 = (1-methylsulfonyl)piperidin-4-yl)amino and the other substituents are as in Compound A).

The compound is prepared according to Example 11 but using as reagent (1-methylsulfonyl)piperidin-4-one).

HPLC (Method A2): rt =14.0 min.

MS: m/z = 742.2 (MH^+).

EXAMPLE 16: cyclo{Suc[1-(R)-(1-aminosulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 = (1-aminosulfonyl)piperidin-4-yl)amino and the other substituents are as in Compound A).

The compound is prepared according to Example 1 but using as reagent (1-aminosulfonyl)piperidin-4-one.

HPLC (Method A2): rt =13.5 min.

MS: m/z = 743.2 (MH^+).

EXAMPLE 17: cyclo{Suc[1-(R)-(piperazin-1-yl)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of formula I wherein R4 = piperazin-1-yl and the other substituents are as in Compound A.

The compound is prepared according to Example 1 but using as reagent N-Boc iminodiacetaldheyde, carrying on the reaction for 16 h and removing the protective group N-Boc with TFA in dichloromethane. The so obtained product is purified by preparative HPLC (Method P2).

1H-NMR (DMSO-d6, 500 MHz): d 2.39 (1H, dd, J = 10.2, 12.4 Hz); 2.65-2.79 (5H, m); 2.79-2.91 (3H, m); 2.99-3.15 (6H, m); 3.22-3.48 (m, overlapping the water signal); 3.51 (1H, dd, J = 4.4, 10.1 Hz); 3.95-4.04 (1H, m); 4.08-4.18 (2H, m); 6.92 (1H, d, J = 8.7 Hz); 6.98 (1H, m); 7.04-7.11 (2H, m); 7.11-7.28 (10H, m); 7.33 (1H, d, J = 8.1 Hz); 7.32-7.37 (1H, m); 7.44 (1H, d, J = 7.9 Hz); 8.32 (1H, d, J = 7.4 Hz); 8.40 (1H, bs); 8.71 (1H, d, J = 5.0 Hz); 10.82 (1H, d, J = 2.1 Hz).

MS: m/z = 650, MH^+.

EXAMPLE 18: cyclo{Suc[1-(R)-4-methyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of formula I wherein R4 = 4-methyl-piperazin-1-yl and the other substituents are as described in Compound A)

To 50 mg of the compound described in example 17, solved in 2 ml methanol, 10 mg paraformaldeide, 25 mg of sodium cianoborohydride, and 50 µl actic acid are added. The solution is stirred for one night, thereafter the solvent is evaporated, the residue is treated with HCl 0.1N, potassium carbonate up to basic pH and extracted with ethyle acetate, washed with brine and dried on magnesium sulfate. The solvent is evaporated giving 34 mg of crude product which are purified by preparativ HPLC (Method P3).

MS: m/z = 664.5 (MH^+).

HPLC (Method A2): rt =12.4 min.

EXAMPLE 19: cyclo{Suc[1-(R)-4-acetyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 = 4-acetyl-piperazin-1-yl and the other substituents are as described in Compound A)

To 40 mg of the compound described in Example 17, solved in 2 ml acetonitrile and 0.5 ml DMF, 50 µl of acetic anhydride are added; the mixture is stirred for one night, concentrated, poured into water, left under stirring for 30 minutes, added with potassium carbonate up to basic pH; the solution is extracted with ethyle acetate, washed with brine and dried on magnesium sulfate. The solvent is evaporated giving 16 mg of a crude product which is purified by preparative HPLC (Method P4).

MS: m/z = 692.5 (MH^+).

HPLC (Method A2): rt =12.8 min.

EXAMPLE 20: cyclo{Suc[1-(R)-(4-methanesulfonyl-piperazin-1-yl)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 = 4-methanesulfonyl-piperazin-1-yl and the other substituents are as described in Compound A).

The compound described in Example 17 was solved in anhydrous DMF treated with TEA and methanesulfonyl chloride. After 3 h under stirring at room temperature the mixture is purified by preparative HPLC (Method P6).

1H-NMR (DMSO-d6, 500 MHz): d 2.41 (1H,t, J = 11.1 Hz); 2.66-2.81 (3H, m); 2.81-3.00 (5H, m); 2.92 (3H, s); 3.00-3.61 (m, overlapping the signal of water); 3.96-4.07 (1H, m); 4.12 (1H, bs); 4.19 (1H, bs); 6.92 (1H, d, J = 8.6 Hz); 6.98 (1H, t, J = 7.4 Hz); 7.03-7.30 (12H, m); 7.45 (1H, d, J = 7.9 Hz); 7.50 (1H, bs); 8.00-8.60 (1H, bs); 8.75 (1H, bs); 10.82 (1H, s).

MS: m/z = 728 (MH^+).

EXAMPLE 21: cyclo{-Suc[1-(S)-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(compound of general formula I wherein C-R4 has S-configuration, R4 is methanesulfonylamino and the other substituens are as described in compound A)

To a solution of 60 mg of the isomer of Compound A having S-configuration at the C-R4, prepared as described in Example 1(a)-1(h), in 1 ml DMF, at 0°C, 24 ml of N-methylmorpholine and 10 ml of methanesulfonylchloride are added; the solution is left under stirring for 2 and half h. The reaction mixture is concentrated under vacuum, diluted with ethylacetate and washed with an aqueous solution of citric acid (10%), water, saturated solution of $NaHCO_3$ and water in the given order. After drying on Na_2SO_4 and evaporation of the solvent the product is isolated by preparative HPLC.

1H-NMR (DMSO-d6, 500 MHz): d 10.80 (d, J = 1.6, 1H); 8.54 (s broad, 1H); 8.34 (dd, J= 3.8, 8.6, 1H); 7.61 (d, J = 7.6, 1H); 6.90-7.40 (m, 16H); 6.64 (d, J = 9.5, 1H) 4.30-4,38 (m, 1H); 4.25-4.30 (m,1H); 4.00-4.10 (m, 2H); 3.65-3.77 (m, 1H); 3.30-3.35 (m, 1H); 2.97 (s, 3H); 2.58-2.95 (m, 8H).

MS: m/z = 659, MH^+.

Following the same procedure reported above, the following products are obtained.

EXAMPLE 22: cyclo{Suc[1-(R)-methanesulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is methanesulfonylamino and the other substituents are as described for Compound A)

1H-NMR (DMSO-d6, 500 MHz): d 10.83 (d, J = 1.6, 1H); 8.82 (d, J= 4.7, 1H); 8.12 (s broad, 1H); 7.44 (d, J = 7.9, 1H); 6.92-7.42 (m, 16H); 6.82 (d, J = 8.8, 1H) 4.11-4,23 (m, 3H); 4.02 (m, 1H); 3.35 (m, 2H); 2.95 (s, 3H); 2.70-2.95 (m, 6H); 2.34 (dd, J = 9.3, 13.5, 1H).

MS: m/z = 659, MH^+.

EXAMPLE 23: cyclo{Suc[1-(S)-(4-methylbenzen)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein C-R4 has S-configuration, R4 is (4-methylbenzen)sulfonylamino and the other substituents are as described for Compound A)

As starting compound the isomer of Compound A having S-configuration at the C-R4 is us d.

MS: m/z = 735, MH^+.

EXAMPLE 24: cyclo{Suc[1-(R)-(4-methylbenzen)solfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of formula I wherein R4 is (4-methylbenzen)sulfonylamino and the other substituents are as described for Compound A)

1H-NMR (DMSO-d6, 500 MHz): d 10.81 (d, J = 1.5, 1H); 8.68 (d, J = 4.5, 1H); 7.95 (s broad, 1H); 7.90 (d, J = 8.8, 1H); 6.95-7.75 (m, 20H); 6.78 (d, J = 8.9, 1H) 4.17(m, 1H); 4.10 (m,1H); 4.05 (m, 1H); 3.94 (m, 1H); 3.17 (m, 1H); 2.97 (m, 1H); 2.65-2.85 (m, 7H); 2.36 (s, 3H); 2.09 (dd, J = 9.1, 13.5, 1H).

MS: m/z = 735, MH^+.

EXAMPLE 25: cyclo{Suc[1-(S)-(2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein C-R4 has S-configuration, R4 is 2-(4-morpholino)ethylamino and the other substituents are as described for Compound A)

The compound is obtained following the procedure of example 1, but using as starting product the isomer of Compound A having S-configuration at C-R4, and 2-(4-morpholino)acetaldheyde as reagent

1H-NMR (DMSO-d6, 500 MHz): d 2.61-3.87 (15H, m); 3.14 (1H, dd, J = 4.6, 13.9 Hz); 3.19-3.90 (m, overlapping the signal of water); 3.98-4.06 (1H, m); 4.08-4.16 (2H, m); 4.30-4.37 (1H, m); 6.95 (1H, s); 6.99 (1H, m); 7.03-7.10 (2H, m); 7.14-7.31 (11H, m); 7.33 (1H, d, J = 8.1 Hz); 7.37 (1H, d, J = 8.9 Hz); 7.42 (1H, d, J = 7.9 Hz); 8.25 (1H, d, J = 5.2 Hz); 8.52 (1H, d, J = 5.2 Hz); 10.83 (1H, d, J = 2.1 Hz).

MS: m/z = 694, MH^+.

EXAMPLE 26: cyclo{Suc[1-(R)-(2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-(4-morpholino)ethylamino and the other substituents are as described for Compound A)

The compound is prepared according to the procedure of example 1 but using as reagent 2-(4-morpholino)acetaldehyde.

MS: m/z = 694, MH^+.

EXAMPLE 27: cyclo{Suc[1-(R)-(2-furylmethyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of formula I wherein R4 is (2-furylmethyl)amino and the other substituents are as described for Compound A)

The compound is prepared according to the procedure of Example 1 but using as reagent 2-furaldheyde. The so obtained crude was purified by prepartive HPLC (Method P2).

1H-NMR (DMSO-d6, 500 MHz): d 2.39-2.46 (1H, m); 2.69-2.96 (5H,m); 3.02-3.22 (2H, bs); 3.57-3.82 (1H, bs); 4.04, 4.16 e 4.30 (5H, bs); 6.50 (1H, bs); 6.59 (1H, bs); 6.84 (1H, d, J = 7.1 Hz); 6,99 (1H. m); 7.04-7.28 (14H, m); 7.35 (1H, d, J = 8.1 Hz); 7.48 (1H, d, J = 7.8 Hz); 7.74 (1H, bs); 8.81 (1H, bs); 9.22-9.69 (1H, bs); 10.88 (1H, s).

MS: m/z = 661, MH^+.

EXAMPLE 28: cyclo{Suc[1-(R)-cianomethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is cianomethylamino and the other substituents are as described for Compound A)

To 50 mg of Compound A, prepared as described in EXAMPLE 1(a)-(h), solved in 1 ml of DMF, 12 µl of TEA and 6.5 µl of chloroacetonitrile are added; thereafter 15 mg of NaI are added and the mixture is stirred for about 16 h at room temperature. The solution is filtered and purified by preparative HPLC (Method P2).1H-NMR (DMSO-d6, 500 MHz): d 2.34 (1H, dd, J = 7.4, 13.6 Hz); 2.71-2.84 (5H, m); 2.91 (1H, dd, J = 4.3, 13.6 Hz); 3.16-3.27 (2H, m); 3.27-3.60 (m, overlapping the signal of water); 3.66 e 3.74 (2H, ABq, J = 17.5 Hz); 3.96-4.11 (1H, m); 4.11-4.27 (2H, m); 6.77 (1H, d, J = 9.0 Hz); 6.98 (1H, m); 7.03-7.10 (2H, m); 7.14-7.21 (3H, m) 7.21-7.30 (5H, m); 7.34 (1H, d, J = 8.1 Hz); 7.44 (1H, d, J = 7.9 Hz); 7.64 (1H, bs); 7.88 (1H, bs); 8.75 (1H, d, J = 4.9 Hz); 10.83 (1H, d, J = 1.6 Hz).MS: m/z = 620, MH^+.

EXAMPLE 29: cyclo{Suc[1-(R)-2-(4-morpholinoacetyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-(4-morpholinoacetyl)amino and the other substituents are as described for Compound A)

To 21 mg of acid 4-morpholineacetic, solved in 5 ml DMF, 40 mg of 1-hydroxy-benzotriazole and 20 mg of EDCI.HCl are added. The solution is left under stirring for 10' and 60 mg of Compound A are added. After 4 h the solvent is evaporated and the residue is purified by preparative HPLC (Method P2).

1H-NMR (DMSO-d6, 500 MHz): d 2.34 (1H, dd, J = 8.3, 14.2 Hz); 2.71-2.90 (5H, m); 2.97 (1H, dd, J = 4.1, 14.2 Hz); 3.00-3.24 (4H, bs); 3.26-3.53 (m, overlapping the signal of water); 3.79 (6H, bs); 4.00-4.10 (1H,m); 4.13-4.20 (1H, m); 4.20-4.27 (1H, m); 4.59-4.68 (1H, m); 6.79 (1H, d, J = 8.1 Hz); 6.95-7.01 (1H, m); 7.05-7.10 (1H, m); 7.15-7.20 (4H, m); 7.23-7.29 (7H, m); 7.35 (1H, d, J = 8.1 Hz); 7.47 (1H, d, J = 7.8 Hz); 8.04 (1H, bs); 8.60 (1H, d, J = 5.2 Hz); 8.53-8.70 (1H, bs); 10.70 (1H, s).

MS: m/z = 708, MH^+.

According to the same procedure the following compounds are obtained.

EXAMPLE 30: cyclo{Suc[1-(S)-2-(4-morpholinoacetyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-(4-morpholinoacetyl)amino, C-R4 has S-configuration and the other substituents are as described for Compound A)

1H-NMR (DMSO-d6, 500 MHz): d 2.57 (1H,dd, J = 4.4; 15.7 Hz); 2.66-2.85 (7H, m); 2.98-3.59 (bs, overlapping the signal of water); 3.26 (dd, J = 4.4; 14.3 Hz); 3.59-4.03 (6H, m); 4.03-4.15 (2H,m); 4.36 (1H, m); 4.77 (1H, bs); 6.84 (1H, bs); 6.94 (1H, d, J = 2.0 Hz); 6.98 (1H, t, J = 7.2 Hz); 7.07 (1H, t, J = 7.2 Hz); 7.13-7.31 (9H, m); 7.33 (1H, d, J = 8.1 Hz); 7.41 (1H, d, J = 7.8Hz); 8.32 (1H, bs); 8.49 (1H, d, J = 4.8 Hz); 8.86-9.10 (1H, bs); 10.10-10.30 (1H, bs); 10.81 (1H, d, J = 1.7 Hz).

MS: m/z = 708, MH^+.

EXAMPLE 31: cyclo{Suc[1-(S)-(2-tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein C-R4 has S-configuration, R4 is (2-tetrazol-1-yl)acetylamino and the other substituents are as described for Compound A)

As starting compound the isomer of compound A having S-configuration at C-R4 is used.

1H-NMR (DMSO-d6, 500 MHz): d 10.80 (d, J = 2.0, 1H); 9.32 (s, 1H); 8.87 (d, J = 8.0, 1H); 8.52 (d, J= 5.3, 1H); 8.38 (dd, J = 4.0, 8.5 1H); 6.93-7.42 (m, 17H); 6.78 (d, J = 9.3, 1H); 5.27 e 5.30 (spectrum AB, J = 16.6, 2H); 4.76 (m, 1H); 4.35 (m,1H); 4.01-4.13 (m, 2H); 3.73 (m, 1H); 3.25-3.35 (m, 1H); 2.54-2.86 (m, 8H).

MS: m/z = 691, MH^+.

EXAMPLE 32: cyclo{Suc[1-(R)-(2-tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is (2-tetrazol-1-yl)acetylamino and the other substituents are as described for Compound A)

MS: m/z = 691, MH^+.

EXAMPLE 33: cyclo{Suc[1-(S)-(2-(5-mercapto-tetrazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein C-R4 has S-configuration, R4 is (2-(5-mercapto-tetrazol-1-yl)acetylamino and the other substituents are as described for Compound A)

As starting compound the isomer of compound A having S-configuration at C-R4 is used.

1H-NMR (DMSO-d6, 500 MHz): d 10.79 (d, J = 1.8, 1H); 8.79 (d, J = 7.9, 1H); 8.54 (d, J= 5.2, 1H); 8.39 (dd, J = 5.4, 8.2 1H); 7.40 (d, J= 7.8, 1H); 6.96-7.34 (m, 15H); 6.95 (s, 1H); 6.77 (d, J= 9.3, 1H); 4.98 e 5.01 (spectrum AB, J = 16.7, 2H); 4.75 (m, 1H); 4.35 (m,1H); 4.01-4.12 (m, 2H); 3.74 (m, 1H); 3.32-3.35 (m, 1H); 2.63-2.85 (m, 7H); 2.58 (dd, J = 4.8, 15.5, 1H).

MS: m/z = 723, MH^+.

EXAMPLE 34: cyclo{Suc[1-(R)-2-([1,2,4]triazol-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-([1,2,4]triazol-1-yl)acetylamino and the other substituents are as described for Compound A)

HPLC (Method A2): rt =13.8 min.

MS: m/z = 690.2 (MH^+).

EXAMPLE 35: cyclo{Suc[1-(R)- (furan-2-yl)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is (furan-2-yl)carbonylamino and the other substituents are as described for Compound A)

To 50 mg of Compound A solved in 1 ml DMF, 8.5 µl of 2-furanoyl chloride and 12 µl of TEA are added. The solution is stirred 30'. The product is purified by preparative HPLC (Method P6), giving 30 mg of pure compound.

HPLC (Method A2): rt =16.6 min.

MS: m/z = 675.3 (MH^+).

EXAMPLE 36: cyclo{Suc[1-(R)-2-(thiophen-3-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-(thiophen-3-yl)acetylamino and the other substituents are as described for Compound A)

The compound was prepared according to the procedure of Example but using as reagent 2-(thiophen-3-yl)acetic acid.

HPLC (Method A2): rt =17.5 min.

MS: m/z = 705.3 (MH^+).

EXAMPLE 37: cyclo{Suc[1-(R)-(4-morpholino)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH2-C6H5)-CH2NH]}

(compound of general formula I wherein R4 is (4-morpholino)carbonylamino and the other substituents are as described for Compound A)

To a solution of 77 mg of compound A, obtained as described in example 1(a)-1(h), in acetonitrile (2 ml), 36 µl of TEA and, at room temperature, under nitrogen, 16 µl of morpholin-4-carbonylchloride are added. The reaction is carried on for 18 h, the solution is concentrated, and purified by preparative HPLC (Method P6).

37 mg of solid product are obtained.

HPLC (Method A2): rt =14.9 min.

MS (ES+): 694.4 [MH+]

EXAMPLE 38: cyclo{Suc[1-(R)-2-(4-hydroxy-piperidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-(4-hydroxy-piperidin-1-

yl)acetylamino and the other substituents are as described for Compound A)
The compound was prepared according to example 29 but using as reagent 2-(4-hydroxy-piperidin-1-yl)acetic acid.
HPLC (Method A2): rt =11.8 min.

MS: m/z = 722.3 (MH^+).

EXAMPLE 39: cyclo{Suc[1-(R)-2-(4-aminocarbonyl-piperidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}
[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}
(compound of general formula I wherein R4 is 2-(4-aminocarboniy-piperidin-1-yl)acetylamino and the other substituents are as described for Compound A)
The compound was prepared using the procedure of example 29 but using as reagent 2-(4-aminocarbonyl-piperidin-1-yl)acetic acid.
HPLC (Method A2): rt =11.7 min.

MS: m/z = 749.4 (MH^+).

EXAMPLE 40: cyclo{Suc[1-(R)-2-(3-hydroxy-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}
(compound of general formula I wherein R4 is 2-(3-hydroxy-pyrrolidin-1-yl)acetylamino and the other substituents are as described for Compound A)
The compound was prepared according to example 29 but using as ragent 2-(3-hydroxy-pyrrolidin-1-yl)acetic acid.
HPLC (Method A2): rt =11.9 min.

MS: m/z = 708.4 (MH^+).

EXAMPLE 41: cyclo{Suc[1-(R)-2-(2-(S)-hydroxymethyl-pyrrolidin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}
(compound of general formula I wherein R4 is 2-(2-(S)-hydroxymethyl-pyrrolidin-1-yl)acetylamino and the other substituents are as described for Compound A)
The compound was prepared according to example 29 but using as reagent 2-(2-(S)-hydroxymethyl-pyrrolidin-1-yl)acetic acid.
HPLC (Method A2): rt =12.2 min.

MS: m/z = 722.3 (MH^+).

EXAMPLE 42: cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)acetylamino]-Trp-Phe-

[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-(4-methyl-piperazin-1-yl)acetylamino and the other substituents are as described for Compound A)

The compound was prepared according to example 29 but using as reagent 2-(4-methyl-piperazin-1-yl)acetic acid.

HPLC (Method A2): rt =11.4 min.

MS: m/z = 721.5 (MH^+).

EXAMPLE 43: cyclo{Suc[1-(R)-2-(4-methyl-piperazin-1-yl)carbonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-(4-methyl-piperazin-1-yl)carbonylamino and the other substituents are as described for Compound A)

A solution of 40 mg of compound A, obtained as described in EXAMPLE 1(a)-1(h), and 400 µl of DIPEA in THF (0.5 ml), is added, under nitrogen, to a solution of 27 mg of 4-methyl-1-piperazinocarbonyl chloride (prepared as described in C. Jorand-Lebrun et al., Synth. Commun. (1998), 28, 1189) in 0.5 ml of dichloromethane. The solution is stirred for 2 h at room temperature, dried and purified by HPLC (Method P7).

HPLC (Method A2): rt =11.8 min.

MS: m/z = 707.2 (MH^+).

EXAMPLE 44: cyclo{Suc[1-(R)-2-(4-aminosulfonyl-piperazin-1-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-(4-aminosulfonyl-piperazin-1-yl)acetylamino and the other substituents are as described for Compound A)

The compound was prepared according to EXAMPLE 29 but using as reagent 2-(4-aminosulfonyl-piperazin-1-yl)acetic acid.

HPLC (Method A2): rt =12.5 min.

MS: m/z = 786.3 (MH^+)

EXAMPLE 45: cyclo{Suc[1-(R)-2-(1-oxo-thiomorpholin-4-yl)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-(1-oxo-thiomorpholin-4-yl)acetylamino and the other substituents are as described for Compound A)

The compound was prepared according to EXAMPLE 29 but using as reagent 2-(1-oxo-thiomorpholin-4-yl)acetic acid.

HPLC (Method A2): rt =11.7 min.

MS: m/z = 740.4 (MH^+)

EXAMPLE 46: cyclo{Suc[1-(R)-2-(*trans*-4-hydroxy-cyclohexan-1-yl-amino)acetylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is 2-(*trans*-4-hydroxy-cyclohexan-1-yl-amino)acetylamino and the other substituents are as described for Compound A).

The compound was prepared according to EXAMPLE 29 but using as reagent 2-(*trans*-4-hyroxy-cyclohexan-1-yl-amino)acetic acid.

HPLC (Method A2): rt =11.6 min.

MS: m/z = 736.3 (MH^+)

EXAMPLE 47: cyclo{Suc[1-(4-morpholino)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein : X_1 = X_2 = X3 = X_4 = -CO-NH-; R_1 = -CH_2-(indol-3-yl); R_2 = R_3 = -CH_2-C_6H_5; R4 = (4-morpholino)carbonyl; m = 0, f = 1; the C-R_1 and C-R_2 carbon atoms have S-configuration, while C-R_3 has R-configuration)

a) Synthesis of Boc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH_2]

To a solution of Boc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-Z] (1.20 g) in methanol (36 ml) and DMF (14 ml), Pd/C 10% (120 mg) was added. The mixture was stirred and hydrogenated at room temperature and pressure for 2 h. The mixture was filtered and the solid washed with methanol.The leuated were pooled together and evaporated giving a viscous oil which was solubilised in ethylacetate. The resulting solution was washed with water and brine and dried on anhydrous sodium sulfate. By evaporating the organic phase 870 mg of a white solid were obtained.

HPLC (Method A3): rt =11.8 min.

MS (ES+): [MH+] = 584

b) Synthesis of Boc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-[2-(4-nitro-

benzyloxycarbonyl)-4-*tert*-butyl)-succin-1-yl]}.

To a solution of [2-(4-nitro-benzyloxycarbonyl)-succinic acid 4-*tert*-butyl ester (424 mg) in DMF (20 ml), at 0°C, HOBt (490 mg), EDCI.HCl (250 mg) and Boc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH_2] (700 mg) were added. The mixture was reacted for 2 h at room temperature. The solvent was eliminated by evaporation under vacuum an the resulting residue was treated with $KHSO_4$ aq. 5% to give a solid which was filtered, washed with $NaHCO_3$ aq. 5%, water and dried under vacuum on $CaCl_2$ giving 1.05 g of a solid product.

MS (ES+): [MH+] = 919.

HPLC (Method A4): rt =20.3 min.

c) Synthesis of cyclo{Suc[1-(4-nitro-benzyloxycarbonyl)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}

In 20 ml of TFA cooled at 0°C, 1.0 g of Boc-Trp-Phe-{(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-[2-(4-nitro-benzyloxycarbonyl)-4-*tert*-butyl)-succin-1-yl]} was added in small portions.

The mixture was reacted for 30' at 0°C, concentrated under vacuum and diluted with DMF, thereafter evaporated giving an oil which was treated with diethylether giving a solid. The solid was filtered and washed with diethylether giving a yellow amorphous solid which was H-Trp-Phe-{(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-[2-(4-nitro-benzyloxycarbonyl)]-1-succinic acid. 710 mg of product were obtained.

To a solution of 200 mg of H-Trp-Phe-{(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-[2-(4-nitro-benzyloxycarbonyl)]-1-succinic acid in DMF (10 ml), under nitrogen at 0°C, PyBOP (160 mg) and TEA (108 µl) were added; the solution was left under stirring at room temperature for 2 hours and thereafter sampled by HPLC. The solvent was evaporated and the residue was solved in ethylacetate. The organic phase was washed with KHSO4 aq. 5%, NaHCO3 aq. 5%, brine and was dried on anhydrous sodium sulfate. After filtration and evaporation of the solvent 180 mg of a residue were obtained.

This crude was purified by preparative HPLC (Method P8). Two products were obtained (diastereisomers) which were indicated as "fast moving" (fm) and "slow moving" (sm). Obtained 62 mg (fm) and 15 mg (sm).

MS (ES+): [MH+](fm) = [MH+](sm) = 745

HPLC (Method A3): rt(fm) =15.1 min, rt(sm) =15.6 min.

d) Compound cyclo{Suc[1-(carboxy]-Trp-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

The compound cyclo{Suc[1-(4-nitro-benzyloxycarbonyl)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]} "fast moving" (100 mg) was added to a mixture 1:1 of water/isopropanole (3 ml) containing K2CO3 (34 mg). The reaction mixture was reacted for 18 h at room temperature, concentrated, diluted with water and extracted with ethylacetate to eliminate the unreacted product.

The aqueous phase was acidified with HCl 1N up to the formation of a white suspension and extracted with ethylacetate. The organic phase of the second extraction was dried on anhydrous sodium sulfate and evaporated to give 55 mg of a white solid. The product was purified by preparative HPLC (Method P8).

Two products (diastereoisomers) were obtained having a different retention time by HPLC they were defined "fast' moving" (fm') and "slow' moving" (sm').

Obtained 16 mg (fm') e 7 mg (sm').

MS (ES+): [MH+](fm') = [MH+](sm') = 610

HPLC (Method A2): rt(fm') =13.7 min, rt(sm') =15.1 min

d') Compound cyclo{Suc[1-(carboxy]-Trp-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

The compound cyclo{Suc[1-(4-nitro-benzyloxycarbonyl)-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2-NH]} "slow moving" (50 mg) was added to a mixture 1:1 of water/isopropanole (2 ml) containing K2CO3 (17 mg). The reaction mixture was reacted for 24 h at room temperature, concentrated, diluted with water and extracted with ethylacetate to eliminate the unreacted product. The aqueous phase was acidified with HCl 1N up to the formation of a white suspension and extracted with ethylcetate. The organic phase of the second extraction was dried on anhydrous sodium sulfate and evaporated to give 18 mg of a white solid. The product was purified by preparative HPLC (Method P8).

Two products (diastereoisomers) were obtained having different retention time by HPLC , they were defined 'fast' moving" (fm') and "slow' moving" (sm').

Obtained 7 mg (fm') e 6 mg (sm').

MS (ES+): [MH+](fm') = [MH+](sm') = 610

HPLC (Method A2): rt(fm') =13.7 min, rt(sm') =15.1 min

Compound cyclo{Suc[1-(4-morpholino)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]

To a solution of cyclo{Suc[1-(carboxy]-Trp-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]} (product "fast'moving", 20 mg) in DMF (1 ml), HOBT (24 mg), EDCI.HCl (12 mg) and morpholine (10 µl) were added in the given order. After 24 h stirring the reaction mixture was diluted with 3 ml of a mixture water/acetonitrile 80:20 containing 0.1% of TFA and purified by preparative HPLC (Method P5). 7 mg of a white solid were obtained.

MS (ES+): [MH+] = 679

HPLC (Method A2): rt =14.8 min.

With the same procedure the following compound was obtained

EXAMPLE 48: cyclo{Suc[1-(4-hydroxyethyloxyethyl-piperazin-1-yl)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

(compound of general formula I wherein R4 is (4-hydroxyethyloxyethyl-piperazin-1-yl)carbonyl and the other substituents are as described in EXAMPLE 47)

HPLC (Method A2): rt =11.9 min.

MS: m/z = 766.2 (MH^+)

Preparative HPLC Methods

Mobile phase: A = H_2O + 0.1% TFA; B = CH_3CN + 0.1% TFA

Method P1:

Column: Deltapak RP18 10 µ, 100 Å, 19 x 300 mm

Gradient from A:B = 75:25 to A:B = 15:85 in 120 min

Flow rate: 15 ml/min

l = 220, 270 nm

Method P2:

Column: Symmetry RP18 7 µ 100 Å, 19 x 300 mm

Gradient from A:B = 75:25 to A:B = 15:85 in 120 min

Flow rate: 15 ml/min

l = 220, 270 nm

Method P3:

Column: Vydac RP18 20 µ, 22 x 250 mm

Gradient from A:B = 90:10 to A:B = 30:70 in 120 min

Flow rate: 15 ml/min

l = 220, 270 nm

Method P4:

Column: Symmetry RP18 7 µ 100 Å, 19 x 300 mm

Gradient from A:B = 85:15 to A:B = 25:75 in 60 min

Flow rate: 15 ml/min

l = 220, 270 nm

Method P5:

Column: Vydac RP18 20 µ, 22 x 250 mm

Gradient from A:B = 80:20 to A:B = 20:80 in 120 min

Flow rate: 20 ml/min

l = 240 nm

Method P6:

Column: Symmetry RP18 7 µ 100 Å, 19 x 300 mm

Gradient from A:B = 80:20 to A:B = 50:50 in 60 min, then from A:B = 50:50 to A:B = 20:80 in 120 min.

Flow rate: 15 ml/min

l = 220, 270 nm

Method P7:

Column: Symmetry RP18 7 µ 100 Å, 19 x 300 mm

Gradient from A:B = 83:17 to A:B = 23:77 in 120 min

Flow rate: 15 ml/min

l = 220, 270 nm

Method P8:

Column: Delta Pak^{TM}, C18, 10 µ, 100 Å, 19 x 300 mm

Gradient from A:B = 75:25 to A:B = 20:80 in 120 min

Flow rate: 15 ml/min

l = 220, 270 nm

Analytical HPLC Methods

Mobile phase: A = H_2O + 0.1% TFA; B = CH_3CN + 0.1% TFA

Method A1:

Column: Symmetry C_{18} 5m, 100 Å, 3.9 x 150 mm

Gradient from A:B = 80:20 to A:B = 14:86 in 20 min followed by A:B = 14:86 for 6 min

Flow rate: 1 ml/min

l = 220 nm

Method A2

Column: Luna 5µ, C8(2), 100Å, 4.6 x 250 mm

Gradient from A:B = 80:20 to A:B = 20:80 in 20 min

Flow rate: 1 ml/min

l = 220, 270 nm

Method A3:

Column: Symmetry C_8 5m, 100 Å, 3.9 x 150 mm

Gradient from A:B = 80:20 to A:B = 20:80 in 20 min

Flow rate: 1 ml/min

l = 220, 270 nm

Method A4:

Column: Symmetry C_8 5m, 100 Å, 3.9 x 150 mm

Gradient from A:B = 80:20 to A:B = 20:80 in 20 min followed by A:B = 20:80 for 6 min

Flow rate: 1 ml/min

l = 220, 270 nm

Abbreviations: For the nomenclature of the amino acids and corresponding abreviations reference is made to IUPAC-IUB Joint Commission on Biochemical Nomenclature(Eur. J. Biochem. 1984, 138, 9); if not otherwise specified the aminoacids are in the S-configuration. The other abbreviation used are: aq. = aqueous solution; Bzl = benzyl; DMF = dimethylformamide; EDCI = 1-(3-dimethylaminopropyl)3-ethylcarbodiimide; Fmoc = fluorenylmethyloxycarbonyl; PyBOP = benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; TEA = triethylamine; TFA = trifluoroacetic acid; Z = Cbz = N-benzyloxycarbonyl, Boc = tert-butoxycarbonyl; -Suc- = succinyl; DIEA = N,N-diisopropylethylamine; DMF = N,N-dimethylformamide; NKA = neurokinin A; HOBt = 1-

hydroxybenzotriazole; rt = retention time; THF = t trahydrofuran. The numbering of the substituents on the succinic group indicated as -Suc(1-NH_2)- is realised with R_4 = NH2 and X_3 and X_4 = CONR.

Biological Activity

The compounds described in the present invention act as antagonists on the NK2 receptor of tachykinins

The biological activity was tested in three different functional tests in vitro using rabbit pulmonary arteria (RPA), hamster trachea (HT) and rat urinary bladder (RUB) according to the methods described by Maggi C.A. et al. Br. J. Pharmacol. 1990, 100, 588, D'Orleans-Juste P. et al. Eur. J. Pharmacol. 1986, 125, 37 e Maggi C.A. et al. J. Pharmacol. Exp. Ther. 246, 308, 1988. The affinity of the compounds for the human NK2 receptor was evaluated in a test of binding using membranes of CHO (Chinese hamster ovary) cells transfected with the NK-2 receptor of human ileum and the radioligand [^{125}I]NKA (Amersham, specific activity 2000 Ci/mmol) at the concentration of 100 pM in studies of competition. The examined compounds were tested in a range of concentration comprised between 0.01 nM and 10mM. After incubation (30 min., 20°C) the samples were filtered and the radioactivity was determined using a gama-counter.

The data collected by functional studies are expressed as pA_2 (Arunlakshana O. and Schild H.O., Br. J. Pharmacol. Chemother. 1959, 14, 45) and those deriving from studies of binding are expressed as pKi (-log Ki calcolated with the program LIGAND: Munson P.J. et al. Anal. Biochem. 1980, 107, 220).

The compounds of the invention showed good activity in all the above said tests with values of pA_2 up to 9.5 and values of pKi up to 10.6

Activity Table

Compound (EXAMPLE)	pKi	pA2		
		RPA	HT	RUB
WO9834949; ex 27	8.5	7.8	8.5	
WO9834949; ex 34	8.6	7.8	8.5	8.0
WO9834949; ex 35	8.6	8.4	8.5	
WO9834949; ex 36	8.7	7.9		
WO9834949; ex 37	8.8			8.2
WO9834949; ex 39	8.8			
WO9834949; ex 40	7.9	7.6	7.5	
WO9834949; ex 44	8.2	7.8	7.9	
ex. 1	10.2	9.2	9.1	
ex. 3	9.7	8.8		9.0
ex. 5	10.6		9.0	9.1
ex. 7	9.8			8.8
ex. 14	9.0			
ex. 16	10.3			9.5
ex. 31	9.2	8.7		
ex. 32	9.3			9.0
ex. 34	9.5			9.0
ex. 38	9.9			9.1
ex. 39	9.3			9.2
ex. 40	9.7			8.9
ex. 48	9.2			9.0